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Review

Molecular mechanisms of the impact of smoke-oxidants

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ABSTRACT

Tobacco smoke is a source of many xenobiotics and free radicals. Reactive oxygen species can affect the body both directly and indirectly, through the activation of both signalling pathways and transcription factors (NF-κB and AP-1).

One of the most important signalling cascades which can affect the oxidants in smoke are mitogen-activated protein kinases (MAPK). The mechanism of MAPK pathways activation by reactive oxygen species depends on the stimulation of specific tyrosine kinases and protein tyrosine phosphatases inactivation. An activated MAP protein can initiate AP-1 signalling and interact with many other transcription factors. The components of tobacco smoke with oxidation-reduction properties can have an effect on NF-κB signalling. Binding of NF-κB and AP-1 with DNA is a complicated process, in which coactivators exhibiting internal histone acetyltransferase activity are involved. The balance between histone deacetylases and acetylases is important for the regulation of inflammatory response in the lungs. Tobacco smoke causes increased acetylase activity and decreased deacetylase activity in epithelial lung cells. The result is an increase in the activation of NF-κB and AP-1.

Oxygen free radicals from tobacco smoke can change the redox status of cells, which can in turn induce the activation of transcription factors, chromatin remodelling and intensified genes transcription for inflammatory mediators.

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Abbreviations: AP-1, activator protein 1; ATF, activating transcription factor; COX-2, cyclooxygenase-2; CRE, cAMP response element; CREB, cAMP response element-binding protein; DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; GM-CSF, granulocyte-macrophage colony stimulating factor; HAT, histone acetyltransferase; HDAC, histone deacetylases; IKK, IκB kinase; IL, interleukin; I-κBα, NF-κB inhibitor; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinases; MEKK, mitogen-activated protein kinases kinases kinases; MIP-1/2, macrophage inflammatory protein; MKPs, MAPK phosphatase; NF-κB, Nuclear factor κB; NLS, nuclear localization signal; Nrf2, nuclear factor-erythroid 2-related factor 2; PGE_2, prostaglandin E_2; PKCδ, protein kinase C δ; PTPs, protein tyrosine phosphatase; ROS, reactive oxygen species; TNFα, tumor necrosis factor-alpha.

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1. Introduction

Tobacco smoke is one of the most well-known factors inducing a variety of inflammatory diseases as well as cancer (diseases of the respiratory tract, cardiovascular system, urinary tract and digestive system) (Chu et al., 2013; Esakky et al., 2012; Liu et al., 2008; Valenti et al., 2013). Nearly forty carcinogens, such as polycyclic aromatic hydrocarbons, aromatic amines, nitrosamines, heterocyclic amine, heavy metals, were identified from tobacco smoke (Derry et al., 2013). These chemicals generate free radicals and disturb intracellular antioxidant mechanisms (Amin et al., 2003).

Reactive oxygen species (ROS) may affect the body both directly and indirectly, through the activation of signal transduction pathways and of transcription factors, or through products of oxidation such as isoprostanes and 4-hydroxy-2-nonenal. Both nuclear factor κB (NF-κB) and activator protein 1 (AP-1) are known transcription factors sensitive to oxidation-reduction processes, and they can be activated by oxidants (Simone et al., 2011). NF-κB and AP-1 regulate the transcription of genes responsible for proteins synthesis, including pro-inflammatory cytokines such as IL-8, IL-6, TNF-α, IL-12 and macrophage inflammatory protein (MIP-1/2) (Reddy et al., 2012; Simone et al., 2011; Swenson et al., 2011; Yang et al., 2013). The objective of this work was to review on the molecular mechanisms of inflammation related to tobacco smoke.

2. The role of reactive oxygen species in signal transduction. Effect of oxidants on MAPK signalling

Oxidants exist in tobacco smoke may play a role in the development of lung inflammation by affecting the signalling cascades of mitogen-activated protein kinases (MAPK) (EC 2.7.12.2). The reactive oxygen species contained in tobacco smoke can stimulate the phosphorylation and activation of extracellular signal-regulated kinase (ERK), p38 MAPK and c-Jun N-terminal kinase (JNK). JNK and p38 MAPK play an important role in the regulation of inflammation (Chang and Karin, 2001; Chialda et al., 2005; Eynott et al., 2003; Foronjy and D'Armiento, 2006; Tamura et al., 1998). JNK mediates phosphorylation of the transcription factor NAFTc, which increases the production of IL-4 and induces differentiation of Th2 cells. Kinase p38 may exacerbate inflammation in the lungs by increasing expression of intercellular adhesion of molecule-1, TNF-α and MIP-2 leading to chemotactic enhancement of both neutrophils and monocytes in the lungs (Foronjy and D'Armiento, 2006; Nick et al., 2000; Tamura et al., 1998).

The mechanism of MAPK pathways activation by ROS depends on the stimulation of specific tyrosine kinases, such as epidermal growth factor receptor (EGFR). Oxidizing factors present in tobacco smoke may induce dimerization and autophosphorylation of EGFR. This causes stimulation of the extracellular signal-regulated kinase activator kinases (MEK1), their phosphorylation factors (Raf-1, Ras), and mitogen-activated protein kinases kinases kinases (MEKK). MEKK can phosphorylate and activate MAPK proteins (Fig. 1) (Chen et al., 2001; Foronjy and D'Armiento, 2006; Zhuang and Schnellmann, 2004). Oxidants can maintain MAPK in an activated state through inactivation (oxidation of cysteine residues in the catalytic centre) of MAPK phosphatase (MKPs). The oxidation of MKPs, a type of protein tyrosine phosphatases (PTPs), leads to a decrease in their activity and maintenance of MAPK activity (Foronjy and D'Armiento, 2006). Stimulated MAPK proteins can activate c-jun and initiate AP-1 signalling, and they can interact with many other transcription factors, such as NF-κB. This leads to the genes induction which stimulates the influx of inflammatory cells into the lungs (Foronjy and D'Armiento, 2006).

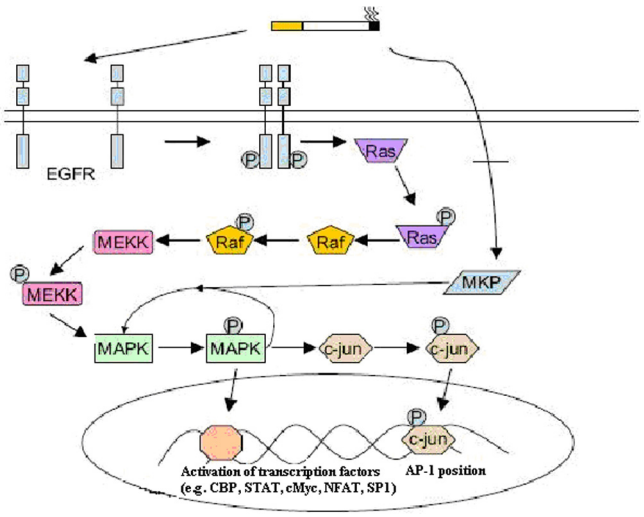

Fig. 1. Influence of tobacco smoke oxidants on MAPK signalling (based on Foronjy and D'Armiento, 2006). EGFR – epidermal growth factor receptor, Ras, Raf – phosphorylating factors, MEKK – MAPK kinases kinases kinases, MAPK – mitogen-activated protein kinases, MKP – MAPK phosphatase, c-jun – subunit of the AP-1, P – phosphorylated.

3. Activation of NF-κB by smoke oxidants

NF-κB is an important transcription factor belonging to the Rel proteins – eukaryotic transcription factors. It is activated by various inducers, including hormones, growth factors, viruses, chemicals, ROS, reactive nitrogen species and cytokines. The nuclear transcription factor κB can regulate the expression of more than 150 genes that encode proteins involved in immune response. These include 27 genes responsible for coding cytokines and chemokines, such as IL-6, IL-1β, TNF-α, granulocyte-macrophage colony stimulating factor (GM-CSF), MCP-1, and IL-8 (Foronjy and D'Armiento, 2006; Simone et al., 2011; Yang et al., 2013). NF-κB regulates the protein expression of the major histocompatibility complex involved in antigen presentation and adhesion molecules that are necessary for adhesion of neutrophils and their passage through blood vessel walls (Foronjy and D'Armiento, 2006).

NF-κB activity is regulated by the cytoplasmic degradation of I-κBα inhibitor (Simone et al., 2011). A classical pathway of NF-κB activation involves the phosphorylation of I-κBα by Akt/phosphoinositide 3-kinase (EC 2.7.1.137) and MAPK, as well as the release of I-κBα from p65 and p50 subunits of NF-κB, which are displaced to the nucleus and can modulate gene expression. These processes are accompanied by activation of the I-κBα gene by NF-κB, and the resultant synthesis and transfer of unphosphorylated I-κBα to the nucleus, which binds to NF-κB and moves back into the cytoplasm (Bar-Shai et al., 2006).

Studies have indicated that factors with oxidation-reduction properties can have an impact on NF-κB signalling. Both the products of lipid peroxidation and a decrease in the amount of reduced glutathione (GSH) can induce ubiquitination and subsequent proteasome degradation of IκB. Reactive oxygen species contained in tobacco smoke are able to activate NF-κB through a variety of mechanisms (Fig. 2) (Foronjy and D'Armiento, 2006). Oxidants can activate MAPK proteins, which are able to phosphorylate and activate the IκB kinase (IKK) (EC 2.7.11.10). Hydrogen peroxide can also activate IKK directly by phosphorylation of serine residues in the activation loop. Both of these pathways lead to IκB degradation by the proteasome, causing exposure of nuclear localization signal (NLS), transfer of NF-κB to the nucleus and binding to DNA, which results in the transcription of inflammatory genes (Foronjy and D'Armiento, 2006).